REMARKS

In an office action, claims 26-29 and 32-40 have been rejected. In response, Applicants provide the herein declaration under 37 C.F.R. 1.132 and remarks. Claims 26-29 and 32-40 are pending examination. Reconsideration is respectfully requested.

Rejections Under §103

Claims 26-30, 32-35 and 38-40 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Curiel et al. (U.S. 6,824,771) in view of Xu et al. (Human Gene Therapy, 1997; 8:177-185). Applicants respectfully disagree with the rejection.

According to the Examiner, Curiel et al. teaches a conditionally replicative recombinant adenovirus which has a functional E1B-19k and is E1B-55k-deleted or is Ea1A-deleted/modified and comprises a therapeutic gene operatively linked to a promoter. The Examiner recognizes that Curiel et al. does not teach that p53 is one of the therapeutic proteins. Rather, Curiel et al. uses thymidine kinase as an exemplary therapeutic gene.

Xu et al. is cited by the Examiner in an attempt to make up for the deficiencies with Curiel et al. The Examiner contends that it would have been obvious to substitute the particular anti-cancer protein, p53 from Xu et al., in the adenovirus of Curiel et al.

For the following reasons, Applicants disagree with the Examiner's line of reasoning:

In order to support a rationale that the combination of elements described in Xu et al. and Curiel et al. is obvious, such combination of elements must yield predictable results. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739-40 (2007). In addition, "predictable results" refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739-40 (2007). DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314 (Fed. Cir. 2009). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

Applicants have provided a detailed explanation in their previous responses as to why the claimed combination would not have been predicted by a skilled person, nor would a skilled person have had a reasonable expectation of success. See, e.g., Response to Office Action, November 8, 2010, at pages 10-12.

The Examiner has found Applicants' arguments of record unpersuasive. In response, Applicants submit herewith a signed declaration by Dr. Frank McCormick, which supports Applicants arguments that the combination of elements described in Xu et al. and Curiel et al. leads to unpredictable results. Dr. McCormick submits that the unexpected discovery that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy is

highly novel and not predictable from previous research publications, including Xu et al., Curiel et al., and Lin et al. See McCormick Declaration, at, e.g., points 3 and 8.

As submitted in Applicants' previous response, it was expected from the prior art that restoration of functional p53 in a replication competent adenovirus would suppress viral replication. See Response to Office Action, November 8, 2010, at page 10. This result was suggested by Hermiston and Kuhn (Cancer Gene Therapy, 2002; 9:1022-1035) and is based on the observation that p53 is actively degraded during viral replication, and adenoviruses that fail to degrade p53 are defective for replication in normal primary human cells (O'Shea et al, Cancer Cell, 2004). This view was re-enforced recently by O'Shea and coworkers (Soria et al, Nature 2010 – a copy is attached to the McCormick Declaration as Exhibit B) who showed that adenoviral E4 proteins contribute to inactivation of p53 during infection, in addition to the well-known effect of E1B 55K on p53 degradation.

Therefore, restoration of functional p53 would be expected to suppress virus replication in a replication competent adenovirus rather than enhancing it. See McCormick Declaration, at point 5.

Furthermore, as submitted in Applicants' previous response, it was not expected that p53 expressed in a replication competent adenovirus would remain functional. Response to Office Action, November 8, 2010, at page 11. Adenoviruses shut down host protein synthesis and

synthesis of viral genes expressed from certain early promoters. It was therefore unexpected that p53 could remain functional (documented in van Beusechem et al., Cancer Research 2002; 62:6165-6171) and promote expression of downstream genes. The recent work of Soria et al. (*supra*) underscores the fact that adenoviruses encode multiple mechanisms to eradicate and inactivate p53 during infection.

Therefore, the activity demonstrated by the instant invention was therefore unexpected for several distinct reasons. See McCormick Declaration, at point 6.

Although the idea that direct, forced, expression of p53 in a p53-negative tumor cell promotes growth arrest, or cell death, has been well established for many years, this effect is clearly distinct from the novel role of p53 in promoting virus replication, as discovered in the instant application. The importance of the instant invention is based on the presumption that clinical efficacy depends on robust virus replication and infection of multiple tumor cells, rather than direct killing of a single transduced cell by a non-replicating viral vector. See McCormick Declaration, at point 7.

The Examiner has also recognized this distinction in the roles of p53 when stating that "the state of the art indicates that p53 dependent apoptosis is prevented through the action of the E1B proteins". See Office Action, July 31, 2006, at page 7. However, figure 6 of the present application demonstrates that conditionally replicating adenovirus expressing both p53 and E1B-

55 kDa effectively kills human cancer cells. In contrast to the teachings of the prior art, the effects of the present application are due to a novel role of p53 in promoting virus replication. See McCormick Declaration, at point 7.

For at least the foregoing reasons, it is submitted that the combination of elements described in Xu et al. and Curiel et al. would not have been expected to work for its intended purpose. The effect of the combination as recited in the claims could not be predicted and was not obvious. Indeed, the art taught away from the present invention as the combination was thought to be ineffective. See McCormick Declaration, at points 3-8.

In view of the above remarks, reconsideration and withdrawal of the rejection based on Curiel et al. in view of Xu et al. is respectfully requested.

Claims 36-37 stand rejected under §103 as allegedly being unpatentable over Curiel et al., in view of Xu et al., as applied to claims 26 and 35 above, and further in view of Lin et al. (Cancer Res. Oct 15, 2000. 60:5895-5901). Applicants traverse the rejection.

Lin et al. is relied on for teaching a mutant form of human p53. However, Lin et al. is silent regarding the effect of restoration of functional p53 in a replication competent adenovirus. Lin et al. is also silent regarding the novel role of p53 in promoting virus replication, as discovered in the instant application. The disclosure of Lin et al. thus fails to remedy the

deficiency that the combination of elements described in the cited references would not have been expected to work for its intended purpose.

The effect of the combination as recited in claims 36-37 could not be predicted and was not obvious. Indeed, the art taught away from the present invention as the combination was thought to be ineffective. See McCormick Declaration, at points 3-8.

In view of the above remarks, reconsideration and withdrawal of the rejection based on Curiel et al. in view of Xu et al., and further in view of Lin et al. is respectfully requested.

It is now believed that the application is in condition for allowance. If the Examiner believes a telephone discussion would be beneficial to resolve any outstanding issue, he is invited to contact the undersigned without hesitation.

Respectfully submitted,

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